[Cited Reference 2]

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Title of Invention: A film - coated granule and the process for the preparation thereof

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What Is Claimed:

[Claim 1] A film - coated granule having a medicament melt - out rate controlling film containing a spherical granule containing a medicament, and an ethyl cellulose, a plasticizing agent and a medicament melt - out rate controlling substance around the outer side of said granule, characterized in that the film - coating agent for forming the medicament melt - out rate controlling film is a water - dispersion body containing a spherical solid particle consisting of ethyl cellulose as the main component and substantially having a diameter of 1 $\mu$ m or smaller, a plasticizing agent and a medicament melt - out rate controlling substance and further that the strength of the film made of this dispersion body is 0.08 gf or greater.

[Claim 2] A film - coated granule as claimed in Claim 1, characterized in that the spherical granule containing the medicament consists of a medicament and a spherical nucleus particle and further that the nucleus particle is a spherical particle containing 30 percent by weight or more of crystalline cellulose.

[Claim 3] A film - coated granule as claimed in Claim 1 or Claim 2, characterized in that the medicament melt - out rate controlling substance is one or more kinds selected from a hydroxy propyl cellulose, a hydroxy propyl methyl cellulose, a carboxy methyl cellulose, polyvinyl alcohol and polyvinyl pyrroridone which is contained in the medicament melt - out rate controlling film in the amount range of 15 percent by weight to 30 percent by weight.

[Claim 4] A film - coated granule as claimed in Claim 1, Claim 2 or Claim 3, characterized in that the thickness of the medicament melt - out rate controlling film is 30 $\mu$ m or greater.

[Claim 5] A film - coated granule as claimed in Claim 1, Claim 2, Claim 3, or Claim 4, characterized in that the particle size distribution is substantially in the

range of 75 to 600 $\mu$ m.

[Claim 6] A process for the preparation of a film - coated granule having a medicament melt - out rate controlling film containing a spherical granule containing a medicament, and an ethyl cellulose, a plasticizing agent and a medicament melt - out rate controlling substance around the outer side of said granule, characterized in that the film - coating agent for forming the medicament melt - out rate controlling film is a water - dispersion body containing a spherical solid particle consisting of ethyl cellulose as the main component and substantially having a diameter of 1 $\mu$ m or smaller, a plasticizing agent and a medicament melt - out rate controlling substance, and further that by the use of a rolling fluid type coating apparatus, the spherical granule is coated with a medicament melt - out rate controlling film.

[Claim 7] A process for the preparation of a film - coated granule as claimed in Claim 6, characterized in that the strength of the medicament melt - out rate controlling film is 0.08 gf or greater.

[Claim 8] A process for the preparation of a film - coated granule as claimed in Claim 6 or Claim 7, characterized in that the spherical granule containing the medicament consists of the medicament and the spherical nucleus particle, and that the nucleus particle is such a type of spherical granule that may contain 30 percent by weight or greater of crystalline cellulose.

[Claim 9] A process for the preparation of a film - coated granule as claimed in Claim 6, Claim 7 or Claim 8, characterized in that the medicament melt - out rate controlling substance is one or more kinds selected from a hydroxy propyl cellulose, a hydroxy propyl methyl cellulose, a carboxy methyl cellulose, polyvinyl alcohol and polyvinyl pyrroridone which is contained in the medicament melt - out rate controlling film in the amount range of 15 percent by weight to 30 percent by weight.

[Claim 10] A process for the preparation of a film - coated granule as claimed in Claim 6, Claim 7, Claim 8 or Claim 9, characterized in that the film coating agent is sprayed in the tangent direction of the rolling action of the rolling fluid type coating apparatus.

Detailed Explanation Of The Invention

[0001]

[Technical Field To Which The Invention Pertains]

The present invention relates to a granule in which the melt - out rate of a medicament is controlled and the process for the preparation thereof. To be more particular, it relates to a spherical granule containing a medicament to which a medicament melt - out rate controlling film is applied.

[0002]

[Conventional Techniques] In medical preparations, the melt - out rate of a medicament (a medically effective component of a medical preparation) is

controlled. Such a type of medical preparation is called a gradually released preparation, or a effect - holding preparation or a tonic preparation and is so designed as to melt out the total amount of the medicament in the range of several hours to ten and several hours.

[0003] As the examples of using a water - disperesiion body of ethyl cellulose as the film coating agent for the purpose of preparing a gradually releasing medical preparation, the followings are known;

Blending of an annealing agent (water - soluble high molecule) (refer to Official Patent Gazette of National Phase PCT Publication No. Sho. 55 - 500709)

Blending of fine pore - forming agent (refer to Official Patent Gazette of Japanese Laid - Open patent Publication No. Hei. 4 - 2756189)

Blending of oidragid (phonetic) (refer to Official Patent Gazette of Japanese Laid - Open patent Publication No. Sho. 57 - 109716)

Blending of a solid particle (talc and starch) (refer to Official Patent Gazette of Japanese Laid - Open patent Publication No. Hei. 2 - 3608) and so on.

[0004] However, the conventional methods used to have defects that as the melt - out amount increases, the melt - out rate decreases and further that they were inferior in the time elapse stability.

[0005]
[Problems Which The Invention Tries To Solve] The present invention is intended to provide such a type of film coated granule in which the rate of melt - out is almost constant irrespective of the melt - out time and is excellent in the time elapse stability of the melt - out time thereof and the process for the preparation thereof.

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[0009] The spherical nucleus particle to be used in the present invention is preferred to be provided with the above - mentioned natures, and further to have a water - absorbing capacity in the range of 0.5 to 1.5 g / g, a tapping apparent density of 0.65 g / $cm^3$ or greater, an abrasion degree of 1 percent or lower and a particle distribution in the range of 75 to 600 $\mu$ m. As the example thereof, it is possible to mention [Selfia] CP - 102, CP - 203, CP - 305 made by Asahi Kasei Kogyo K.K. and Nonparel - 105 made by Freund Industry K.K. By the way, the method of measuring the respective properties and so on will be mentioned in detail later.

[0010] The medicament to be used in the present invention is such a type that may be used for treating, preventing and diagnosing the diseases of human - being and also animals, and therefore is not an apparatus nor is it a machine. As the examples thereof, it is possible to mention the followings;

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[0011] As the method of preparing the spherical granule, well known methods can be used, for example, an extruding Merme's method, a method for supporting medicament on the nucleus particle (a modifying particle formation method) can be used. The spherical particle in which a medicament is supported on the outer side and / or inner side of the spherical particle is a preferred embodiment of the present invention.

[0012] In order to facilitate to support the medicament on the spherical nucleus particle, or to prevent the medicament from peeling off in the later processing, or for adjusting the melt - out rate of the medicament, or for the stabilization thereof, it is possible to jointly use the followings to support the medicament; bonding agents, for example, a hydroxy propyl cellulose, a hydroxy propyl methyl cellulose, polyvinyl alcohol and polyvinyl pyrroridone and so on; film coating base agents, for example, a hydroxy propyl methyl cellulose phthalate, a hydroxy propyl methyl cellulose acetate succinate, a carboxy methyl cellulose, ethyl cellulose, an ethyl cellulose water dispersion, an aminoalkyl methacrylate copolymer E, a methacrylic acid copolymer - L, and so on; surface active agents, for example, cane sugar, an aliphatic acid ester, polyoxy ethylene polyoxy propylene glycol, polysolvate, sodium laurosulphate, sugar and so on; shape - forming agents, for example, corn starch, rice starch, sugar powder, crystalline cellulose and so on; decay agents, for example, a low substitution hydroxy propyl cellulose, carmelose (phonetic) calcium, cross carmelose sodium, partially alpharized starch, and so on; inorganic substances, for example, talc, magnesium stearate, light type silica anhydride, synthesized aluminum silicate, titanium oxide and so on; others, for example, crystalline cellulose · carmelose sodium, hardened oil, macrogoal (phonetic) and so on.

[0013] For the purpose of decreasing the irregularities of the coating (supporting) of the medicament and the coating of the medicament release rate controlling film, the provision of a two - layer structure of the medicament and the water - soluble high molecule (for example, a hydroxy propyl methyl cellulose and so on) on the outer side of the spherical nucleus particle (the case of coating a water - soluble high molecule on the outer side of the nucleus particle, and the medicament on the outer side thereof, and the case of coating the medicament on the outer side of the nucleus particle and the water - soluble high molecule on the outer side thereof); and a three - layer structure (the case of coating the water - soluble high molecule on the outer side of the nucleus particle and the medicament of the outer side thereof and further the water - soluble high molecule on the outer side thereof) is a preferred embodiment of the spherical granule of the present invention.

[0014] As the method of supporting the medicament on the spherical nucleus particle, well known methods can be used. As one example thereof, ① a method of spraying a medicament powder (which, if it is necessary, contains a shape - forming agent) simultaneously with continuously spraying a bonding agent aqueous solution, while the spherical nucleus particle is being rolled in the centrifugal fluid type coating apparatus. ② a method of spraying a solution obtained by dissolving or suspending the medicament in the bonding agent aqueous solution, while the spherical nucleus particle is being rolled in the fluid layer coating apparatus (or a rolling fluid type coating machine). ③ a method of adding an aqueous solution of

the medicament and the bonding solution in such an amount that the nucleus particle may be able to absorb, while the spherical nucleus particle is being rolled in the high speed stirring particle forming apparatus; ④ a method of immersing the spherical nucleus particle in the aqueous solution of the medicament and the bonding solution. In any method, if it is necessary, such operations are carried out as drying, and removing the produced particle for the coating with the medicament melt - out rate controlling film.

[0015] The amount of the medicament to be supported is dependent on the amount to be administered. For example, in the case of such a type of medicament that may exhibit a medical effect even with a minute amount, it will be roughly 0.01 percent by weight on the basis of the spherical nucleus particle, while in the case of such a type of medicament that may require a great amount of medicament for exhibiting a medical effect, the amount to be supported will be around 300 percent by weight. The generally usable amount to be supported in the present invention will be in the range of 0.5 to 100 percent by weight. The film coated granule of the present invention has the medicament melt - out rate controlling film containing an ethyl cellulose, a plasticizing agent, and a water - soluble high molecule, on the outside of the spherical granule.

[0016] The ethyl cellulose to be used in the present invention is those, in which the content of the ethos radical (- OCR $H_6$) to be measured according to Guide to General Chapters / General Test and Assays / < 431 > Methopxy Determination Method (with the proviso that 1 mL of 0.1 N sodium thiosulfate solution corresponds to 0.7510 mg of ethoxy radical) of The United States Pharmacolia 23 (USA) is in the range of 41.0 to 51.0 percent by weight.

[0017] The plasticizing agent to be used in the present invention is such a type of substance that may decrease the glass transition temperature and the minimum film forming temperature of ethyl cellulose. As the examples thereof, it is possible to mention monoglyceride acetylate, triethyl citrate, triacetine, dibutyl sebacate, dimethyl sebacate, mid - chain aliphatic acid triglyceride, acetyl triethyl citrate, dibutyl adipate, an oleic acid, oleynol and so on. The selection of the plasticizing agent is greatly dependent on the solubility of the medicament and the design of the medical preparation (the determination of the melt - out rate and the preservation stability of the medicament). One example will be mentioned. In the case the solubility of the medicament is low, it is possible to decrease the irregularities of the film coating, and therefore it is preferable to use monoglyceride acetylate. In the case the solubility of the medicament is high, it is preferable to use triethyl citrate which makes it possible to lessen the amount of the film coating.
The blend amount is determined in consideration of the minimum film forming temperature, the adhesivity to be caused by the heat softening of the film (influence to the film coating operation), preservation stability and so on. However, the blend amount will be roughly in the range of 10 to 70 percent by weight on the basis of 100 percent by weight of ethyl cellulose, and preferably in the range of nearly 25 to 50 percent by weight.

[0018] As the medicament melt - out rate controlling substance to be used in the present invention, those generally used for medical preparations can be used and as

the examples thereof, it is possible to mention a methyl cellulose, a hydroxy ethyl cellulose, a hydroxy propyl cellulose, a hydroxy propyl methyl cellulose, a carboxy methyl cellulose; ols containing the organic aliphatic or aromatic diol, and polyols such as dextrin, pluran (phonetic), polyvinyl alcohol, polyvinyl pyrroridone and so on; urea, dimethyl sulfone, nicotinamide, Arabian rubber, sodium alginate, propylene glycol alginate ester, xanthane gum, an amino alkyl methacrylate copolymer, a methacrylate copolymer, alkali metal salts, alkali earth metal salts, transition metal salts, saccharides such as glucose and lactose, sorbitol, mannitol, trehalose and so on. In the present invention, one or more kinds of these are used. Among these, the water - soluble high molecule is melted out gradually from the medicament melt - out rate controlling film when the film - coated granule comes in contact with gastric juice and so on, whereby small pores are formed in the film. That is, the diffusion resistance of the film goes down with the elapse of time (the melt - out of the medicament) .

[0019] Normally in the case of the gradually releasing type granule of the film control type to be used in the present invention, the medicament melts out of the film (body fluid) in proportion to the time, while the concentration of the medicament aqueous solution within the film keeps a saturated state. That is, the melt - out rate is constant, but the melt - out rate decreases in accordance with the decrease of the concentration of the aqueous solution, which was a defect thereof. This fact is against the object of the gradually releasing medical preparation which is [to maintain the in - blood concentration of the medicament to be constant for a long period of time], and this was one of the points to be improved. However, in the present invention, as mentioned before, the diffusion resistance of the film gradually decreases, and therefore, even if the concentration of the medicament aqueous solution within the film decreases, the melt - out rate is not decreased, thus making it possible to melt out the whole amount of the medicament in proportion to the elapse of time.

[0020] Further, it is important that in the case of the gradually releasing type medical preparation, the melt - out rate of the medicament is restricted and also it is necessary for the irregularities between the products and the change with time to be sufficiently small, and the limit of the irregularities in the melt - out rate is considered to be within the range where the exhibition of the medical effects is deemed to be in the equal level. As the standard thereof, it is mentioned, for example, in [A Guideline with regard to the Design and the Evaluation of Gradually Releasing Medical Preparations (Orally dosed agent)], (Edited by the Association of Japan Official Codex, 1992 Edition of the Guideline for the Manufacture of Medical Preparations, pages 107 to 112 (by Medical Press) ). The blending of the water - soluble high molecule will result in the increase of the medicament melt - out rate of the film after all, and therefore, in order to obtain the desired gradual release (the time for melting out the whole amount of the medicament), it is necessary to increase the amount of the film coating, that is, to increase the thickness of the medicament melt - out rate controlling film. When the thickness of the film is increased, the mechanical strength is increased and the preservation stability can be improved.